Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Previously presented) A system comprising:

(a) a therapeutic protein formulation that has been modified for enhanced cellular uptake properties; and

(b) an implantable catheter system to physically deliver said therapeutic protein formulation across the blood-brain barrier of patients for the purpose of treating said patients having neurological diseases of the central nervous system, and

(c) a pump that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region,

wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation, and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease, genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof; and

wherein at least some proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins being modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein, and wherein the conjugation comprises a linker species existing between said therapeutic protein and said transport aid, said linker being a streptavidin-biotin complex linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

2. (Original) The system of claim 1, wherein the neurological diseases treated are selected from the group consisting of lysosomal storage diseases, protein deficiency diseases, enzyme deficiency diseases, inborn errors of metabolism, neurodegenerative diseases, and combinations thereof.

3. (Original) The system of claim 1, wherein said neurological diseases are inborn errors of metabolism selected from the group consisting of gangliosidosis, sphingolipidosis, glycoprotein disorders, glycogen storage diseases, mucolipidosis, mucopolysaccharidosis, cholesterol ester storage disease, farber lipogranulomatosis, galactosialidosis type I, galactosialidosis type II, neuronal ceroid lipofuscinosis, and combinations thereof.

4. (Original) The system of claim 1, wherein said neurological diseases are selected from the group consisting of Fragile X Syndrome, Parkinson's disease, Alzheimer's disease, and combinations thereof.

5. (Original) The system of claim 1, wherein the therapeutic protein formulation comprises enzymes providing for enzyme replacement therapy.

6. (Original) The system of claim 5, wherein the enzymes are selected from the group consisting of beta-glucosidase, glucocerebrosidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, saposin B, alpha-galactosidase A, beta-galactosidase, beta-hexosaminidase A, beta-hexosaminidase A and B, alpha-L-fucosidase, alpha-D-mannosidase, beta-D-mannosidase, N-aspartyl-betaglucosaminidase, alpha-glucosidase, LAMP-2, glycogen branching enzyme, neuraminidase, phosphotransferase, alpha-L-iduronidase, iduronate-2-sulfatase, heparan-N-sulfatase, alpha-N-acetylglucosaminidase, acetylCoA:N-acetyltransferase, N-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, beta-galactosidase, N-acetylgalactosamine 4-sulfatase, beta-

glucuronidase, lysosomal acid lipase, acid cholesteryl ester hydrolase, acid ceramidase, N-acetyl-alpha-D-galactosaminidase, palmitoyl protein thioesterase, and combinations thereof.

7. (Original) The system of claim 1, wherein the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF, FMRP, and combinations thereof.

8. (Canceled)

9. (Previously presented) The system of claim 1, wherein said modified proteins have been modified by incorporating into their structure amino acid sequences providing for an intrinsic transport aid.

10. (Original) The system of claim 9, wherein said modified proteins are fusion proteins.

11. (Canceled)

12. (Previously presented) The system of claim 1, wherein the transport aid comprises at least a portion of a species selected from the group consisting of recombinant human melanotransferrin, p97, tetanus toxin fragment C, endogenous lectins, biotin, and combinations thereof.

13. (Canceled)

14. (Previously presented) The system of claim 1, wherein said linker is selected from the group consisting of peptide linkages, disulfide linkages, and combinations thereof.

15. (Canceled)

16. (Original) The system of claim 1, wherein said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation.

17. (Original) The system of claim 16, wherein the integrity and activity of the protein formulation is achieved by the addition to said therapeutic protein formulation, at least one species operable for maintaining a desired pH.

18. (Original) The system of claim 1, wherein said implantable catheter system is implanted so as to deliver said therapeutic protein formulation to regions selected from the group consisting of intrathecal, intraparenchymal, intracerebroventricular, and combinations thereof.

19. (Original) The system of claim 1, further comprising an inlet for the introduction of therapeutic protein formulation to the implanted catheter system.

20. (Original) The system of Claim 1, further comprising a reservoir to contain said therapeutic protein formulation prior to delivery.

21. (Original) The system of claim 20, wherein said reservoir is implantable and refillable.

22. (Canceled)

23. (Previously presented) The system of claim 1, wherein the pump comprises an integrated reservoir.

24. (Previously presented) The system of claim 1, wherein said pump is implantable.

25. (Original) The system of claim 1, wherein the implantable catheter system comprises at least one branched catheter permitting delivery to at least two separate regions using one primary catheter line.

26. (Original) The system of claim 25, wherein the branched catheter is bifurcated.

27. (Canceled)

28. (Previously presented) A system comprising:

(a) a means for providing for a therapeutic protein formulation that facilitates cellular uptake of proteins within said formulation; and

(b) a means of physically bypassing the blood-brain barrier, via an implantable catheter system, so as to deliver said therapeutic protein formulation to target cells for the purpose of treating neurological diseases of the central nervous system; and

(c) a pump that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region,

wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation, and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease, genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof; and

wherein at least some proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins being modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein, and wherein the conjugation comprises a linker species existing between said therapeutic protein and said transport aid, said linker being a streptavidin-biotin complex linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

29. (Original) The system of claim 28, wherein the neurological diseases to be treated are selected from the group consisting of lysosomal storage diseases, protein deficiency diseases, enzyme deficiency diseases, inborn errors of metabolism, neurodegenerative diseases, and combinations thereof.

30. (Original) The system of claim 28, wherein said neurological diseases are inborn errors of metabolism selected from the group consisting of gangliosidosis, sphingolipidosis, glycoprotein disorders, glycogen storage diseases, mucolipidosis, mucopolysaccharidosis, cholesterol ester storage disease, farber lipogranulomatosis, galactosialidosis type I, galactosialidosis type II, neuronal ceroid lipofuscinosis, and combinations thereof.

31. (Original) The system of claim 28, wherein said neurological diseases are selected from the group consisting of Fragile X Syndrome, Parkinson's disease, Alzheimer's disease, and combinations thereof.

32. (Original) The system of claim 28, wherein the therapeutic protein formulation comprises enzymes providing for enzyme replacement therapy.

33. (Original) The system of claim 32, wherein the enzymes are selected from the group consisting of beta-glucosidase, glucocerebrosidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, saposin B, alpha-galactosidase A, beta-galactosidase, beta-hexosaminidase A, beta-hexosaminidase A and B, alpha-L-fucosidase, alpha-D-mannosidase, beta-D-mannosidase, N-aspartyl-betaglucosaminidase, alpha-glucosidase, LAMP-2, glycogen branching enzyme, neuraminidase, phosphotransferase, alpha-L-iduronidase, iduronate-2-sulfatase, heparan-N-sulfatase, alpha-N-acetylglucosaminidase, acetylCoA:N-acetyltransferase, N-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, beta-galactosidase, N-acetylgalactosamine 4-sulfatase, beta-glucuronidase, lysosomal acid lipase, acid cholesteryl ester hydrolase, acid ceramidase, N-acetyl-alpha-D-galactosaminidase, palmitoyl protein thioesterase, and combinations thereof.

34. (Original) The system of claim 28, wherein the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF, FMRP, and combinations thereof.

Claims 35-43 (Canceled)

44. (Original) The system of claim 28, wherein said therapeutic protein formulation is formulated to help maintain the integrity and activity of the protein formulation.

45. (Original) The system of claim 28, wherein the means of physically bypassing the blood-brain barrier so as to deliver said therapeutic protein formulation to target cells comprising positioning said implanted catheter system so as to deliver said therapeutic protein formulation in a manner selected from the group consisting of intrathecally, intraparenchymally, intracerebroventricularly, and combinations thereof.

46. (Original) The system of claim 28, wherein said implanted catheter system comprises a branched catheter.

47. (Original) The system of claim 46, wherein the branched catheter is a bifurcated catheter to allow for the delivery of protein formulation to two regions with a single catheter.

48. (Original) The system of claim 28, further comprising a reservoir to contain said protein formulation prior to delivery.

49. (Original) The system of claim 48, wherein said reservoir is implantable and refillable.

50. (Canceled)

51. (Previously presented) The system of claim 28, wherein the pump comprises an integrated reservoir.

52. (Previously presented) The system of claim 28, wherein said pump is implantable.

53. (Canceled)

54. (Previously presented) A system comprising:

(a) a therapeutic protein formulation; and

(b) an implantable catheter system to physically deliver said therapeutic protein formulation across the blood-brain barrier at a programmed delivery rate for the purpose of treating patients diagnosed with at least one neurological disease of the central nervous system; and

(c) a pump that pumps said therapeutic protein formulation through said implantable catheter system to at least one targeted region,

wherein the pump provides for a programmable delivery rate of the therapeutic protein formulation, and wherein the delivery rate is selected based on factors selected from the group consisting of specific neurological disease, genetic sequence of the patient's gene encoding for the protein to be delivered, body weight, and combinations thereof; and

wherein at least some proteins within said therapeutic protein formulation have been modified to comprise a transport aid that provides for enhanced cellular uptake of said modified proteins, said modified proteins being modified by conjugation to a transport aid that facilitates the cellular uptake of said therapeutic protein, and wherein the conjugation comprises a linker species existing between said therapeutic protein and said transport aid, said linker being a streptavidin-biotin complex linking the protein with the transport aid in a pH-dependent manner wherein the therapeutic protein and transport aid remain operably linked in a neutral pH environment, and the therapeutic protein disassociates at an acidic pH.

55. (Previously presented) The system of claim 54, wherein the neurological disease treated is selected from the group consisting of lysosomal storage diseases, protein deficiency diseases, enzyme deficiency diseases, inborn errors of metabolism, neurodegenerative diseases, and combinations thereof.

56. (Original) The system of claim 54, wherein said at least one neurological disease is an inborn error of metabolism selected from the group consisting of gangliosidosis, sphingolipidosis, glycoprotein disorders, glycogen storage diseases, mucolipidosis, mucopolysaccharidosis, cholesterol ester storage disease, farber lipogranulomatosis, galactosialidosis type I, galactosialidosis type II, neuronal ceroid lipofuscinosis, and combinations thereof.

57. (Original) The system of claim 54, wherein said at least one neurological disease is selected from the group consisting of Fragile X Syndrome, Parkinson's disease, Alzheimer's disease, and combinations thereof.

58. (Original) The system of claim 54, wherein the therapeutic protein formulation comprises enzymes providing for enzyme replacement therapy.

59. (Original) The system of claim 58, wherein the enzymes are selected from the group consisting of beta-glucosidase, glucocerebrosidase, acid sphingomyelinase, galactocerebrosidase, arylsulfatase A, saposin B, alpha-galactosidase A, beta-galactosidase, beta-hexosaminidase A, beta-hexosaminidase A and B, alpha-L-fucosidase, alpha-D-mannosidase, beta-D-mannosidase, N-aspartyl-betaglucosaminidase, alpha-glucosidase, LAMP-2, glycogen branching enzyme, neuraminidase, phosphotransferase, alpha-L-iduronidase, iduronate-2-sulfatase, heparan-N-sulfatase, alpha-N-acetylglucosaminidase, acetylCoA:N-acetyltransferase, N-acetylglucosamine 6-sulfatase, galactose 6-sulfatase, beta-galactosidase, N-acetylgalactosamine 4-sulfatase, beta-glucuronidase, lysosomal acid lipase, acid cholesteryl ester hydrolase, acid ceramidase, N-acetyl-alpha-D-galactosaminidase, palmitoyl protein thioesterase, and combinations thereof.

60. (Original) The system of claim 54, wherein the therapeutic protein formulation comprises proteins selected from the group consisting of GDNF, FMRP, and combinations thereof.

61. (Canceled)

62. (Previously presented) The system of claim 54, wherein said modified proteins have been modified by incorporating into their structure amino acid sequences providing for an intrinsic transport aid.

63. (Original) The system of Claim 62, wherein said modified proteins are fusion proteins.

64. (Canceled)

65. (Previously presented) The system of claim 54, wherein the transport aid comprises at least a portion of a species selected from the group consisting of recombinant human melanotransferrin, p97, tetanus toxin fragment C, endogenous lectins, biotin, and combinations thereof.

66. (Previously presented) The system of claim 54, wherein the conjugation comprises a linker species existing between said therapeutic protein and said transport aid.

67. (Canceled)

68. (Original) The system of claim 54, wherein said therapeutic protein formulation has been formulated to help maintain the integrity and activity of the protein formulation.

69. (Original) The system of claim 54, wherein said implantable catheter system is implanted so as to deliver said therapeutic protein formulation to regions selected from the group consisting of intrathecal, intraparenchymal, intracerebroventricular, and combinations thereof.

70. (Original) The system of claim 54, further comprising an inlet for the introduction of therapeutic protein formulation to the implanted catheter system.

71. (Original) The system of claim 54, further comprising a reservoir to contain said therapeutic protein formulation prior to delivery.

72. (Original) The system of claim 71, wherein said reservoir is implantable and refillable through a subcutaneous inlet.

73. (Original) The system of claim 54, wherein the programmable pump comprises an integrated reservoir.

74. (Original) The system of claim 54, wherein said programmable pump is implantable.

75. (Original) The system of claim 54, wherein the implantable catheter system comprises at least one branched catheter permitting delivery to at least two separate regions using one primary catheter line.

Claims 76-128 (Canceled)

129. (Previously presented) The system of claim 1, wherein the streptavidin-biotin complex is an engineered variant of an avidin or streptavidin and biotin pair, wherein the therapeutic protein is linked to either the avidin or the biotin, and the transport aid is linked to the other of the avidin or biotin.

130. (Previously presented) The system of claim 129, wherein the linker is a streptavidin and 2'-iminobiotin complex linking the therapeutic protein with the transport aid in a pH-dependent manner, wherein the therapeutic protein and transport aid are operably linked in a neutral pH environment of the cerebral spinal fluid of the patient, and disassociate in lysosomal departments or other acidic intracellular organelles of the patient.

131. (Previously presented) The system of claim 28, wherein the streptavidin-biotin

complex is an engineered variant of an avidin or streptavidin and biotin pair, wherein the therapeutic protein is linked to either the avidin or the biotin, and the transport aid is linked to the other of the avidin or biotin.

132. (Previously presented) The system of claim 131, wherein the linker is a streptavidin and 2'-iminobiotin complex linking the therapeutic protein with the transport aid in a pH-dependent manner, wherein the therapeutic protein and transport aid are operably linked in a neutral pH environment of the cerebral spinal fluid of the patient, and disassociate in lysosomal departments or other acidic intracellular organelles of the patient.

133. (Previously presented) The system of claim 54, wherein the streptavidin-biotin complex is an engineered variant of an avidin or streptavidin and biotin pair, wherein the therapeutic protein is linked to either the avidin or the biotin, and the transport aid is linked to the other of the avidin or biotin.

134. (Previously presented) The system of claim 133, wherein the linker is a streptavidin and 2'-iminobiotin complex linking the therapeutic protein with the transport aid in a pH-dependent manner, wherein the therapeutic protein and transport aid are operably linked in a neutral pH environment of the cerebral spinal fluid of the patient, and disassociate in lysosomal departments or other acidic intracellular organelles of the patient.

135. (New) The system of claim 1, wherein delivery of said therapeutic protein formulation across the blood-brain barrier of patients comprises delivery to the central nervous system (CNS), and wherein the system provides for enhanced transcytosis of therapeutic proteins into cells.

136. (New) The system of claim 28, wherein delivery of said therapeutic protein formulation across the blood-brain barrier of patients comprises delivery to the central nervous

system (CNS), and wherein the system provides for enhanced transcytosis of therapeutic proteins into cells.

137. (New) The system of claim 54, wherein delivery of said therapeutic protein formulation across the blood-brain barrier of patients comprises delivery to the central nervous system (CNS), and wherein the system provides for enhanced transcytosis of therapeutic proteins into cells.

138. (New) The system of claim 1, wherein delivery of said therapeutic protein formulation is *in vivo*.

139. (New) The system of claim 28, wherein delivery of said therapeutic protein formulation is *in vivo*.

140. (New) The system of claim 54, wherein delivery of said therapeutic protein formulation is *in vivo*.